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Hauser, Tobias U ; Rüttsche, Bruno ; Wurmitzer, Karoline ; Brem, Silvia ; Ruff, Christian C ; Grabner, Roland H

Abstract: BACKGROUND A small but increasing number of studies suggest that non-invasive brain stimulation by means of transcranial direct current stimulation (tDCS) can modulate arithmetic processes that are essential for higher-order mathematical skills and that are impaired in dyscalculic individuals. However, little is known about the neural mechanisms underlying such stimulation effects, and whether they are specific to cognitive processes involved in different arithmetic tasks. METHODS We addressed these questions by applying tDCS during simultaneous functional magnetic resonance imaging (fMRI) while participants were solving two types of complex subtraction problems: repeated problems, relying on arithmetic fact learning and problem-solving by fact retrieval, and novel problems, requiring calculation procedures. Twenty participants receiving left parietal anodal plus right frontal cathodal stimulation were compared with 20 participants in a sham condition. RESULTS We found a strong cognitive and neural dissociation between repeated and novel problems. Repeated problems were solved more accurately and elicited increased activity in the bilateral angular gyri and medial plus lateral prefrontal cortices. Solving novel problems, in contrast, was accompanied by stronger activation in the bilateral intraparietal sulci and the dorsomedial prefrontal cortex. Most importantly, tDCS decreased the activation of the right inferior frontal cortex while solving novel (compared to repeated) problems, suggesting that the cathodal stimulation rendered this region unable to respond to the task-specific cognitive demand. CONCLUSIONS The present study revealed that tDCS during arithmetic problem-solving can modulate the neural activity in proximity to the electrodes specifically when the current demands lead to an engagement of this area.

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Neurocognitive effects of transcranial direct current stimulation in arithmetic learning and performance: a simultaneous tDCS-fMRI study

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Abstract

Background: A small but increasing number of studies suggest that non-invasive brain stimulation by means of transcranial direct current stimulation (tDCS) can modulate arithmetic processes that are essential for higher-order mathematical skills and that are impaired in dyscalculic individuals. However, little is known about the neural mechanisms underlying such stimulation effects, and whether they are specific to cognitive processes involved in different arithmetic tasks.

Methods: We addressed these questions by applying tDCS during simultaneous functional magnetic resonance imaging (fMRI) while participants were solving two types of complex subtraction problems: repeated problems, relying on arithmetic fact learning and problem-solving by fact retrieval, and novel problems, requiring calculation procedures. Twenty participants receiving left parietal anodal plus right frontal cathodal stimulation were compared with 20 participants in a sham condition.

Results: We found a strong cognitive and neural dissociation between repeated and novel problems. Repeated problems were solved more accurately and elicited increased activity in the bilateral angular gyri and medial plus lateral prefrontal cortices. Solving novel problems, in contrast, was accompanied by stronger activation in the bilateral intraparietal sulci and the dorsomedial prefrontal cortex. Most importantly, tDCS decreased the activation of the right inferior frontal cortex while solving novel (compared to repeated) problems, suggesting that the cathodal stimulation rendered this region unable to respond to the task-specific cognitive demand.

Conclusions: The present study revealed that tDCS during arithmetic problem-solving can modulate the neural activity in proximity to the electrodes specifically when the current demands lead to an engagement of this area.

Keywords

transcranial Direct Current Stimulation (tDCS), functional Magnetic Resonance Imaging (fMRI), arithmetic, mathematics, simultaneous tDCS-fMRI

Introduction

Arithmetic competencies are essential for educational and professional success [1]. They depend on at least two different skills: the application of arithmetic problem-solving procedures (e.g., when solving a complex subtraction problem) and the learning as well as retrieval of stored arithmetic facts (e.g., the multiplication table). However, a considerable number of individuals in our societies do not successfully acquire these skills; impairments of arithmetic competencies are widespread and highly detrimental for those affected. It is estimated that almost every fifth schoolchild suffers from a mathematical learning disorder (developmental dyscalculia; DD) [2,3], which drastically lowers the child's school and professional expectations [1]. Despite this high prevalence and importance, remediation programs are still relatively sparse.

Recent advances in the understanding of the neural mechanisms involved in arithmetic problem solving have underscored the potential of non-invasive brain stimulation to enhance arithmetic performance. One of the most promising techniques within non-invasive brain stimulation is transcranial direct current stimulation (tDCS) [4]. With tDCS, weak electrical currents are applied through two electrodes attached to the subject's head. Although the exact mechanisms of how tDCS affects neural tissues underneath the electrodes are still not completely understood [4–6], it is assumed that neural populations below the anode are rendered more excitable, whereas neural populations underneath the cathode show lower excitability [7–9]. However, it should be noted that while enhancing effects of anodal tDCS in cognition are consistently reported, the effects of cathodal tDCS are less clear [10,11]. Nevertheless, tDCS has not only become useful for investigating brain function in diverse domains, but is also starting to be used for the treatment of various neuropsychiatric disorders [12].

In the arithmetic domain, first studies have demonstrated that tDCS can affect arithmetic performance and learning [13–16]. However, the observed effects strongly depended on the cognitive processes involved in the arithmetic operation as well as the placement of the tDCS electrodes. Solving complex arithmetic problems (two-digit subtractions, typically solved using procedures) were found to be enhanced by anodal tDCS of left but not right or bilateral parietal cortex [13,17]. For solving simple arithmetic problems (which is typically done by fact retrieval), in contrast, the same stimulation had detrimental effects. In addition, it was recently found that anodal stimulation of the parietal cortex led to better arithmetic fact learning of subtraction problems, whereas cathodal stimulation led to an impairment in learning [16].

The specificity of tDCS effects on arithmetic is not surprising, as it is well known that different arithmetic demands recruit different neural populations [18–23]. Solving arithmetic problems by means of procedures involves magnitude processing (e.g., counting, calculation) and recruits a widespread bilateral network including

the intraparietal sulcus (IPS) and medial and inferior lateral prefrontal areas. Learning and retrieving arithmetic facts, on the other hand, primarily activates a left-hemispheric network comprising the angular gyrus (AG), prefrontal cortex and other perisylvian language regions [19,24].

Although much has been learnt in recent years about how we can modulate arithmetic skills by means of tDCS, we still have little knowledge about the mechanisms of how tDCS affects neural activity in different brain regions. It is particularly unclear whether tDCS affects the general baseline activity of a region, or whether it modulates neural activity in a task-related fashion. Moreover, we have little knowledge about the specific brain region where such effects take place and whether they are selective for a specific arithmetic task. A solid understanding of these mechanisms is a prerequisite for the development of targeted and specific intervention programs to treat DD.

To better understand these mechanisms, we here studied the effects of tDCS on arithmetic in 40 healthy subjects using simultaneous tDCS-fMRI, which allows us to determine the brain regions that show tDCS-induced neural activation changes. In two separate groups, we applied a parietal anodal plus frontal cathodal stimulation protocol or a matched sham stimulation protocol, respectively. To determine the task specificity of the stimulation effects, we administered two types of arithmetic demands: (a) learning and retrieving arithmetic facts and (b) solving complex arithmetic problems by means of procedures. In our fMRI analysis, we assessed whether tDCS had a task-specific effect on brain activity, hypothesizing that such an effect would be largest in areas where we found the biggest effects in our current-flow simulations.

Methods

Participants

A total of 48 adult, right-handed subjects participated in this experiment. They were blinded for the stimulation and were pseudo-randomly allocated to either active or sham stimulation, simultaneously ensuring that the groups were matched for age and gender (active: $22.4y \pm 3.0$, 10 females; sham: $22.4y \pm 3.6$, 10f). All participants were recruited from local universities, fulfilled the local criteria for participating in fMRI and tDCS studies, did not report any history of neurological or psychiatric disorders, and did not consume any psychoactive drugs. However, we did not explicitly control for nicotine use - which can affect stimulation effects [25] – but instead relied on the pseudo-random allocation procedure to balance this factor across groups. Eight of the participants had to be excluded due to various reasons (four in each group; four due to excessive motion during fMRI, four due to poor initial performance or no learning). Participants were reimbursed with 60 CHF for their participation. We collected an additional sample of 24 participants using a different stimulation configuration, which we will report in a separate paper. The study was approved by the ethics committee of the canton of Zurich, and all participants gave written informed consent.

Procedure

We used a MR-compatible tDCS device (Neuroconn GmbH) for applying tDCS while simultaneously recording fMRI (see below). Prior to scanning, we attached the electrodes to the participant's head using sticky 10-20-paste and rubber straps and bandages to ensure direct contact between the electrode and the skin.

Based on our previous studies [13,16,17], we used a tDCS protocol with anodal stimulation of left parietal and cathodal stimulation of right prefrontal areas. We used the same electrode configuration for the active and sham stimulation. The anode (5*7cm) was centred over left parietal electrodes CP5 and P5, which was in proximity of IPS and AG [13,16,17,26]. The cathode (5*10 cm) was positioned over right prefrontal areas placing the electrode supraorbitally (between Fpz and AF8). Because prefrontal areas are known to have a strong inter-individual variability [27,28], we tried to compensate for this issue by choosing a slightly larger electrode. Simulation (cf. below) showed that even this slightly larger electrode still has a strong impact on the tissue underneath. Ideally, one would place a smaller electrode based on each individual's anatomical image. However, due to organisational reasons, we were not able to record a structural image before the stimulation session.

In the active stimulation group, we stimulated the subjects with 1mA for the first 30 minutes of the task (Fig. 1). The sham group was only stimulated for the first 30 seconds, which is known to have no effect on the participant's behaviour despite being indistinguishable by the subject [29]. The current in both groups was ramped over 10 seconds at the beginning and the end of the stimulation. Please note that a stimulation duration of 30 minutes is relatively long compared to other studies, and that a longer stimulation duration can also have inverse effects [30]. Here, we decided to employ this this duration, because we have used similar protocols in previous studies [13,16,17].

Simulations

To investigate the current flow and density induced by our tDCS protocol, we modelled the electrical field with the COMETS Toolbox for MATLAB [31]. COMETS allows investigating current field distributions on the cortical surface employing a finite element head model. The simulation suggested that the current densities under the left parietal electrode were around 0.02 mA/cm², while the effects of the stimulation on the areas underlying right prefrontal electrode exceeded 0.025 mA/cm² (in particular close to the edges of the electrode; Fig. 2).

Experimental task

The participants were presented with complex subtraction problems (two-digit minus two-digit problems; e.g. 53 – 17) during 45 minutes of scanning. To administer two types of arithmetic demands, the subtraction problems were divided into two conditions. In the learning condition, 3 problems (randomly selected from a pool of 27 problems) were presented 40 times over the course of the experiment (i.e., repeated problems). The high number of repetitions elicited fact learning, so that the participants could finally solve these problems by means of fact retrieval. In the no-learning condition, the remaining 24 problems (i.e., novel problems) of the pool were presented only 3 times each to the participants, so that these problems need to be solved by means of procedures rather than fact retrieval. The comparison between both conditions allowed us to specifically investigate the learning and retrieval of arithmetic facts (repeated problems) and the solving of arithmetic problems using procedures (novel problems), irrespective of other time-dependent factors such as fatigue or habituation to the study setting. The composition of repeated and novel problems was matched across stimulation groups (i.e., in each group there was a subject with exactly the same novel and repeated stimuli).

Over the course of the experiment, subjects solved the task in three problem solving sessions of 15 minutes each. Two of the three sessions were performed during tDCS and one after the stimulation. Each session included

16 bundles consisting of three problems. Bundles of repeated and novel problems were alternated, with half the participants starting with repeated problems and half starting with novel problems (i.e., [repeated, novel, ... repeated, novel] or [novel, repeated, ... novel, repeated]). After every bundle, a null trial with a length of 13s was included.

In every trial, the arithmetic problem was presented for 5000ms and subjects were told not to respond during that time. Then, three choice alternatives were presented after a jittered fixation cross (range: 1500 - 4000ms). The participants selected one of the alternatives, and feedback about the correctness of the response was provided: A white frame was shown around the selected alternative and a green frame was shown around the correct alternative (if the selected alternative was correct, only a green frame was shown). This trial structure allowed us to separate response execution and problem solving, resulting in cleaner measures of neural activity elicited by the presented problem. Jittered breaks with fixation crosses (range: 1500 - 4000ms) were inserted before and after the presentation of the problem. Alternative solutions were computed as the correct solution +1, -1, +2, -2, +10, or -10, and were randomly distributed.

To ensure that the subjects learned the solutions to the repeated stimuli, the sessions were interspersed with short learning checks (Fig. 1). Per learning check, each repeated problem was presented four times. The overall trial structure slightly differed from that of the problem solving sessions: The subjects were asked to press a button as soon as they had reached a solution (time limit: 7000ms), no fixation cross was presented between the problem presentation and response selection screens, no correctness feedback was provided and the fixation duration between trials was set so that each trial lasted 10000ms overall (minimal fixation duration was 1000ms).

Behavioural analysis

To investigate the behavioural performance in the learning checks, we analysed both solution rates and reaction times. In contrast, in the three problem solving sessions, we focused on the solution rates, because our fMRI design was optimised to minimize temporal confounds and was therefore insensitive to potential changes in processing speed. We computed repeated-measures ANOVAs with the factors Session (learning checks: 1-4, problem solving sessions: 1-3), Stimulus type (novel, repeated) and Group (active, sham) using SPSS, and applied Greenhouse-Geisser correction if sphericity was violated.

Functional magnetic resonance imaging (fMRI)

The participants were scanned in a 3 T Philips Achieva scanner using a 32 channels head coil. In several pilot studies, we determined a tDCS-setup and an fMRI sequence that had no artifacts in the fMRI images to provide optimal image quality (analysing deformations, signal-to-noise ratios, etc.). Specifically, we used an EPI sequence optimized to minimize signal dropout from the tDCS device (TR=2200ms, TE=30ms, FA=80°, FOV=240x240x111mm, 37 slices, 3mm slice thickness). A total of 1310 volumes plus five initial dummy volumes were recorded over the 45 minutes of scanning. A fieldmap was acquired to account for magnetization inhomogeneities [32]. Additionally, a T1-weighted structural image with 1mm resolution was recorded for normalization purposes.

fMRI data preprocessing

fMRI preprocessing and analysis was carried out in SPM8 (<http://fil.ion.ucl.ac.uk>). Raw EPIs were unwarped using the acquired fieldmap [32]. The realigned EPIs were then normalized using deformation toolbox with flowfields estimated from the structural T1 images (resulting voxel size: 1.5*1.5*1.5mm). Subsequently, the normalized EPIs were spatially smoothed with a kernel of 6mm (FWHM) to fulfil smoothness assumptions underlying random-field theory.

fMRI data analysis

We were mainly interested in the cognitive processes during arithmetic problem solving. For each subject, we thus entered a regressor with the onset of a mathematical problem (stimulus) in an event-related design in the first-level GLM. Each problem solving session of the experiment was modelled as a separate regressor. Moreover, novel and repeated stimuli were modelled in separate regressors. To account for potential confounding events, we additionally added the following regressors as nuisance-regressors: onset of response alternatives, feedback phase, button presses and breathing, pulsatile and movement artifacts [33,34]. For the regressors of interest, only correctly answered trials were used. Incorrect trials were modelled separately as regressors of no interest. The learning checks were also modelled as separate nuisance regressors.

To investigate the main effect of learning (i.e. repeated vs novel problems), we analysed the contrast repeated-novel (and vice versa) condition using one-sample t-tests across all participants and sessions. For the stimulation specific effects, we compared the two groups (active, sham) using t-tests.

We used a family-wise error (peak-FWE) significance threshold of $p < .05$ to account for multiple comparisons in all analyses. We decided on this stringent threshold to ensure strict control for false positives.

Results

Performance during the learning checks

To assess whether the subjects successfully learned the repeated arithmetic stimuli, we interspersed the learning sessions with short learning checks. Both groups showed significant improvements in performance over sessions, but the groups did not significantly differ in their performance (Fig. 3A; solution rates: session $F(3,114)=20.58$, $p<.001$, group $F(1,38)=1.34$, $p=.25$, session *group $F(3,114)=.39$, $p=.76$; reaction times: session $F(3,114)=53.36$, $p<.001$, group $F(1,38)=.65$, $p=.427$, session *group $F(3,114)=.63$, $p=.598$). Thus, both groups learned the repeated stimuli equally well. Additionally, the groups did not differ before the stimulation (first learning check: solution rate: $t(38)=.65$, $p=.521$; reaction times: $t(38)=-1.02$, $p=.312$), showing that both groups started from the same performance level.

Performance during the problem solving sessions

The repeated-measures ANOVA of the solution rates revealed a significant main effect of stimulus type ($F(1,74.2)=35.607$, $p<.001$), demonstrating that repeated stimuli were solved significantly better than novel stimuli (Fig. 3B). There was no significant effect of session ($F(1.7,74.2)=.458$, $p=.606$), meaning that performance did not improve over time. This was due to a ceiling effect of performance from the first session onwards. The main effect of group was not significant ($F(1,38)=1.683$, $p=.202$), which means that both groups did not differ in their overall performance. None of the interactions was significant (session*group: $F(1.7,74.2)=.234$, $p=.753$; stimulus*group: $F(1,74.2)=.933$, $p=.340$; session*stimulus: $F(1.953,74.2)=.009$, $p=.990$; session*stimulus*group: $F(1.953,74.2)=.195$, $p=.823$).

fMRI results

Learning effects

To investigate the neural correlates of learning complex arithmetic facts, we computed the difference in activation between novel and repeated stimuli across all learning sessions. To illustrate learning, we post-hoc split these effects into relative change for novel and repeated stimuli across the sessions.

For repeated minus novel stimuli (across both groups), we found strongly increased activity in a network containing bilateral angular gyri (AG) and medial/lateral prefrontal cortex (Fig. 4A, Table 1). Post-hoc analysis of each session showed an increase in activity in these areas as learning progressed (middle panel). Moreover, it became evident that the activation in the left AG is mainly driven by a stronger relative deactivation for novel

stimuli (right panel); congruent with previous reports [21,35]. Within the repeated stimuli, there was a slight decline in activation strength over sessions (right panel).

Novel compared to repeated stimuli elicited increased activity in a network including bilateral intraparietal sulci (IPS) and dorsomedial prefrontal cortex (dmPFC, Fig. 4B, Table 1). Again, the post-hoc analysis of session showed an increased spread of the activated areas as a function of session (middle panel). The activation in the left IPS (right panel) shows a generally higher activation for novel as compared to repeated stimuli. In both stimuli, a slight decline in activation strength over sessions is evident (right panel).

Stimulation effects

To investigate the neural changes that were caused by tDCS, we compared the differences between active stimulation and sham stimulation in the contrast between novel and repeated problems, as well as for each problem type separately.

No main effect of stimulation group on activation of either repeated or novel stimuli survived FWE-multiple comparison correction. However, there was a significant stimulation-related difference in the contrast novel > repeated problems in the right inferior prefrontal cortex (Fig. 5, Table 2). The opposite contrast did not yield a significant effect. Post-hoc analysis reveals that in the sham group, this region displays a constant deactivation for novel, but not repeated stimuli (right panels). However, in the active stimulation group, this region was unresponsive to stimulus type. This finding suggest that this region is being deactivated when solving complex novel subtractions. The cathodal stimulation of this region, however, seems to render this region unable to respond to the task demands.

Discussion

Transcranial electrical stimulation, such as tDCS, is a promising set of methods for treating patients suffering from neuropsychiatric disorders [8,12]. In the field of arithmetic, several studies have investigated the beneficial effect of tDCS on various aspects of arithmetic problem solving and learning [13,16,17,36]. However, despite first progress, the findings thus far are relatively heterogeneous and different stimulation protocols being beneficial only for a narrow set of cognitive processes and skills. This is not surprising given that many imaging studies demonstrate that these skills rely on distinct neural networks and processes [18–23]. Therefore, a better understanding of the neuro-cognitive effects of particular stimulation protocols is necessary to successfully develop and apply tDCS for the treatment of development dyscalculia and related disorders.

The present study is – to the best of our knowledge – the first study to use simultaneous tDCS-fMRI to advance this endeavour. This method allows us to study the impact of tDCS on arithmetic problem solving and the underlying neural activity.

TDCS did not have a significant effect on task performance. This, however, might be due to the specific task that we employed. In previous studies [13,16,17], we showed that a similar stimulation protocol elicited performance improvements. In comparison to those studies, our task differed in various aspects. First, in order to dissociate the measurement of neural activity from cognitive processes and motor actions, we sacrificed the measurement of reaction times. In addition, performance was close to ceiling due to the relatively long elaboration time before the selection of an answer alternative was required. Moreover, the power of the current task to detect performance differences was lower, as we had to reduce the number of trials due to the requirements of the fMRI. Nevertheless, in line with our previous findings [13,16], the solution rates were slightly better (albeit not statistically significant) in the active tDCS condition. We additionally explored whether performance changes within the active tDCS group were related to activation changes in IFG to assess whether individual differences in tDCS sensitivity was reflected in behaviour. None of these analyses revealed significant results (data not shown), again supporting the relative insensitivity of solution rates in our task.

Our fMRI analysis of learning effects nicely confirmed previous studies investigating arithmetic fact learning [22,35,37]: On the one hand, retrieval of arithmetic facts (solving repeated problems) engaged a fronto-parietal network including the AG and frontal cortex. On the other hand, the application of procedures to solve the novel arithmetic problems most strongly activated a fronto-parietal network containing the IPS.

The analysis of tDCS-specific effects on neural activity revealed a significant change in activation in the right inferior prefrontal cortex. Post-hoc analysis revealed that this region was characterized by a decreased

activation for novel stimuli in the sham group, while no task-dissociation was present in the active tDCS group. The activation for the repeated stimuli was unaffected by tDCS. Our findings suggest that tDCS influences neural activity in a task-specific manner; this supports our assumption that the specificity of a stimulation protocol is due to the dissociable involvement of particular cognitive processes and neural networks. Interestingly, the stimulation-effect is located next to the edge of the cathodal electrode, which was also the one region where our simulation (Fig. 2) predicted the strongest stimulation effects for the frontal electrode. This demonstrates the usefulness and accuracy of simulating current flow using conductance models [31]. However, it also highlights that the current density is not homogeneously distributed under the electrode. The stimulation had a stronger impact on brain regions in proximity to the electrode edges, with a particular effect on gyri rather than sulci. We thus suggest that future studies should use electrode placements based on individuals' brain structures, rather than using larger electrodes to accommodate the inter-individual heterogeneity.

The absence of a task-specific behavioural modulation in the active stimulation condition lends to speculations about the potential causes. Of particular interest is that active tDCS primarily abolished the deactivation for novel stimuli in this region. Given that cathodal tDCS is assumed to hyperpolarize membranes and thus lowers the excitability of a given region [7–9], it might be that this hyperpolarization renders neural populations unable to respond to the input. This would also explain why it cannot react and change its activity to novel stimuli. However, the fact that fMRI measures neural activity only indirectly, via metabolic demands, makes it difficult to confirm such conclusions.

It is also important to highlight that we found a significant stimulation effect in the absence of a behavioural effect. Although not significant, the behavioural performance tended towards an improvement in performance for the active tDCS condition, similar to our previous studies [13,16,17]. This contrasts with the tDCS-induced impairment found in the prefrontal cortex. This discrepancy could be explained by antagonistic effects of the anodal and cathodal electrodes in our setup: the prefrontal cathode had an impairing effect on the brain activity for novel stimuli, and, potentially, on performance. The anodal stimulation of the parietal cortex, however, could have an enhancing effect on performance, as we have shown in previous studies [13,16,17]. This effect might have abolished the prefrontal impairment. However, it is unclear why there was no significant stimulation effect over parietal areas. Future studies are needed to investigate how specific brain areas are affected by particular stimulation protocols.

Although we believe that our study provides important insight into the mechanisms of stimulation-specific effects in arithmetic, it also points to difficulties inherent in the use of simultaneous tDCS-fMRI. The main

problem is that fMRI protocols are by necessity much slower than tasks that are typically used in tDCS studies. The lowered power of a reduced trial number thus makes it more difficult to detect tDCS effects on behaviour. Interestingly, a previous offline fMRI-tDCS study [38] also reported stimulation-specific fMRI results in the absence of behavioural effects. In the present study, we investigated for the first time the effects of tDCS on two types of arithmetic demands (facts and procedures). Future tDCS-fMRI studies, possibly using different stimulation protocols, should be conducted in other numerical domains such as magnitude processing to complement the current findings. Moreover, it would also be interesting to investigate the specificity of the stimulation method and to compare tDCS to other methods, such as transcranial random noise stimulation (tRNS). tRNS over prefrontal areas in particular was found to enhance numerical abilities and is thus of particular interest [39–41]. Likewise, it is also crucial to understand how brain stimulation may relate to individual traits, such as math anxiety [36].

In summary, we found that cathodal frontal tDCS changed the task-specific modulation of the inferior prefrontal cortex during arithmetic problem solving by means of procedures. Additionally, we highlighted the importance of precise knowledge of the networks that are involved in distinct arithmetic processes as well as the need for a better understanding of the neural location affected by a tDCS protocol. Only by accounting for these prerequisites, we will be able to develop efficient and specific treatments of impairments in arithmetic skills.

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Figure captions:

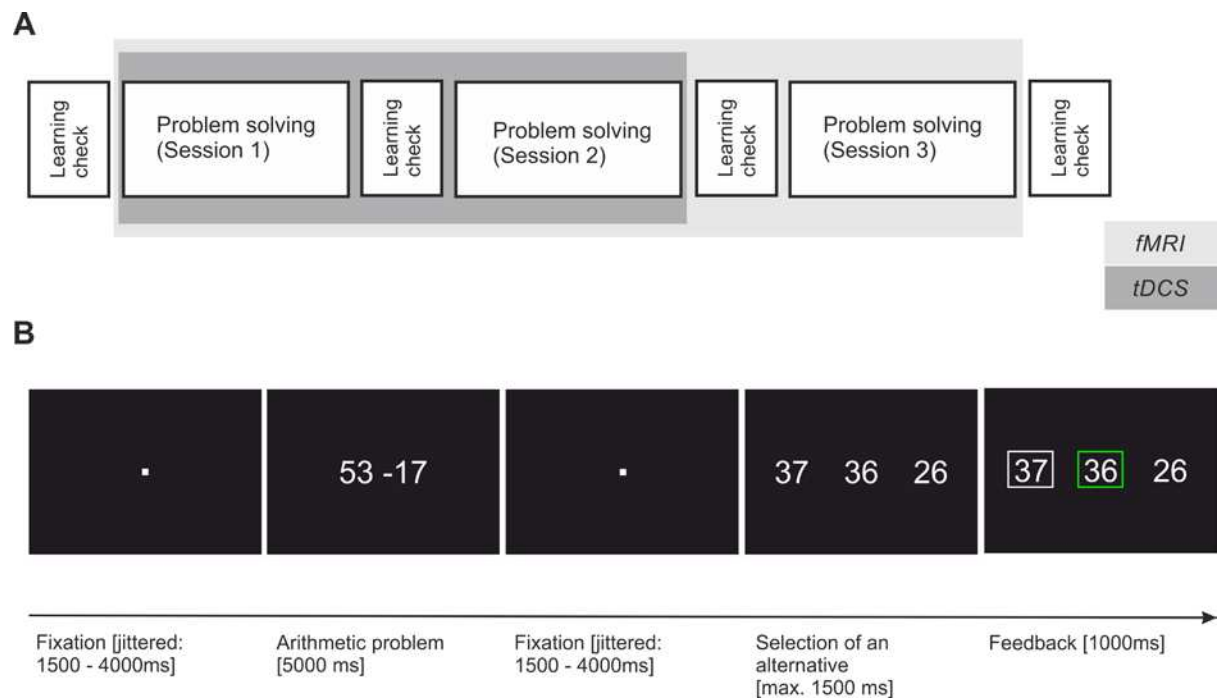


Figure 1: Task and trial structure. (A) Participants solved novel and repeated problems in three problem solving sessions while fMRI was recorded. During the first two sessions, tDCS was applied. The sessions were interspersed with short learning checks to ensure that learning of the repeated stimuli was occurring. (B) During each trial, participants had to solve a complex subtraction which either was presented frequently (repeated problems), or rarely (novel problems). Subjects had to select the correct answer from three possible solutions (white frame) and were given feedback (green frame).

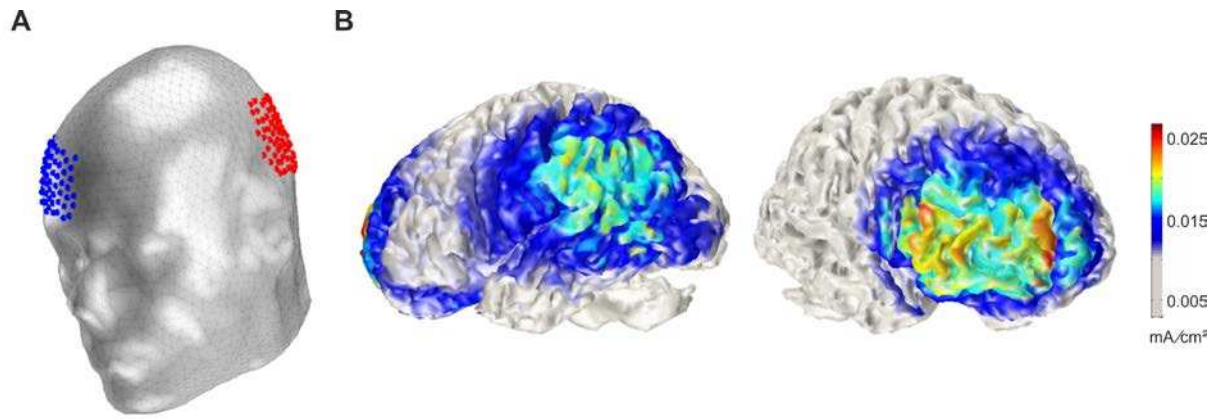


Figure 2: Modelling of current density. (A) Electrode placement displayed on a head-model. The anodal electrode (red) was placed left-parietally, while the cathode (blue) was placed over right prefrontal cortex. (B) Left-hemispheric and right-frontal views of the simulated current density show that both parietal and prefrontal cortex receive elevated currents, with peaks in right prefrontal cortex.

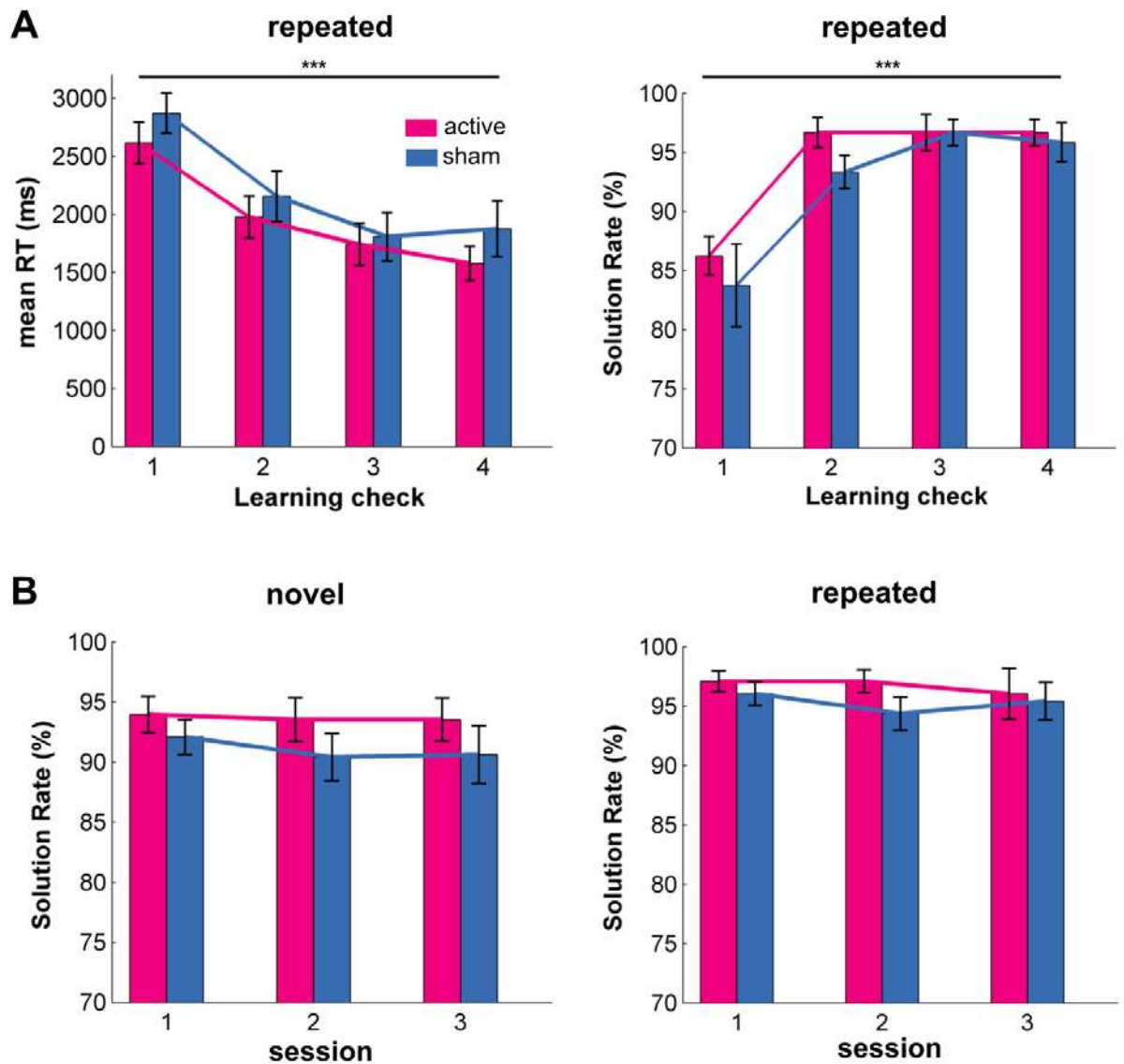


Figure 3: Performance during the experiment. (A) Learning checks assessed performance of repeated stimuli between the learning sessions. These learning checks revealed that both reaction times (left panel) and solution rates (right panel) improved significantly over time. This shows that subjects learned these repeated problems, with no difference between the groups. (B) There were no differences in performance across problem solving sessions or between stimulation groups for both novel (left) and repeated (right) stimuli. Performance for repeated was significantly higher than for novel stimuli. *** $p < .001$; bar plots: mean \pm s.e.m.

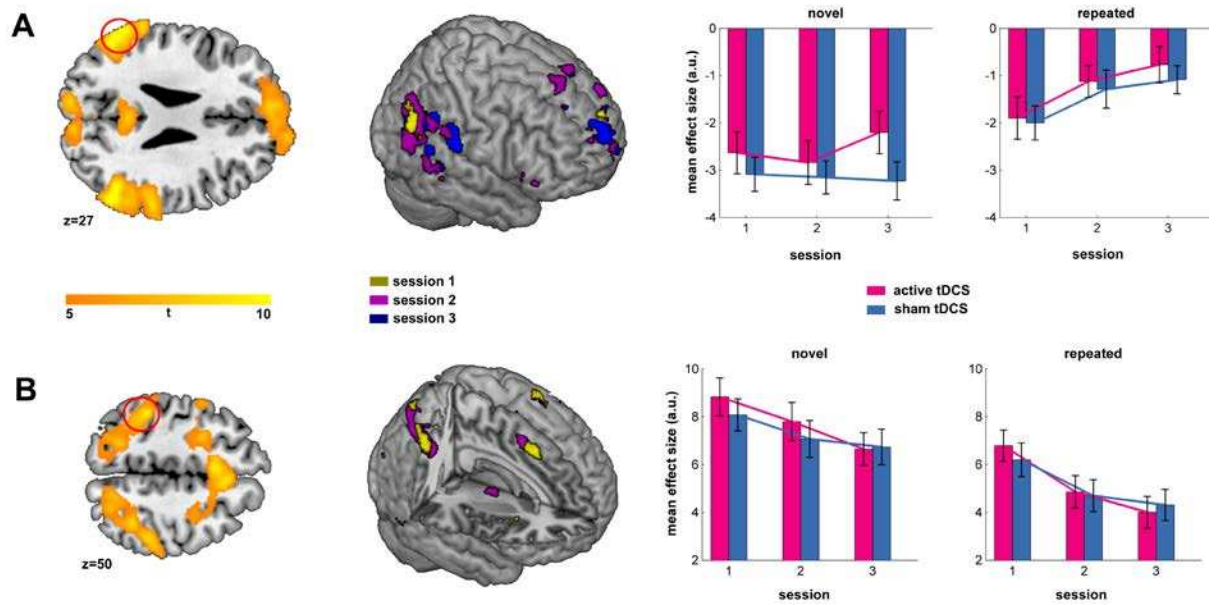


Figure 4: fMRI learning effects. (A) Repeated stimuli activated a network containing angular gyrus (AG; red circle, left panel) and medial and lateral prefrontal areas. The width of these activations (middle panel, shown at $p < .001$, uncorrected) as well as the strength (right panel: IAG) increased over time. These post-hoc bar plots illustrate that novel stimuli lead to a generally stronger deactivation than repeated stimuli. (B) Novel stimuli elicited an increased activation in the intraparietal sulcus (IPS; red circle, left panel) and the dorsomedial prefrontal cortex. Illustrative bar plots show how the IPS is generally more strongly activated by novel stimuli. a.u.: arbitrary units; bar plots: mean \pm s.e.m.

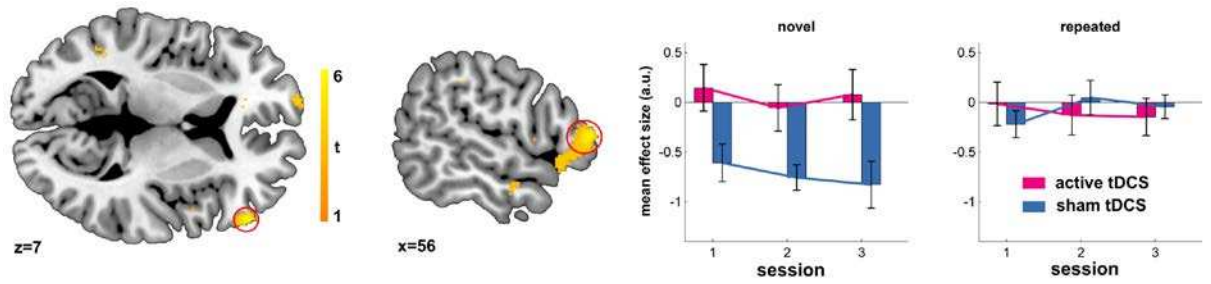


Figure 5: fMRI stimulation effects. tDCS diminishes response to novel stimuli in the right inferior prefrontal cortex (red circle). For illustrative purposes, post-hoc bar plots show that sham stimulation elicited a differential activation in this area for novel and repeated problems, whereas active tDCS eliminated any task-specific modulation. bar plots: mean \pm s.e.m.

Table 1. fMRI learning effects. Novel stimuli elicited increased activity in bilateral IPS and prefrontal cortex, while repeated stimuli caused increased activation in bilateral AG and prefrontal regions. Thresholded at peak-FWE $p < .05$, $k > 50$. AG: angular gyrus; dmPFC: dorsomedial prefrontal cortex; dlPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; PCC: posterior cingulate cortex; PPL: posterior parietal lobe; SFG: superior frontal gyrus.

Contrast	Region	Hemisphere	Cluster size (voxels)	x	y	z	T Score
novel > repeated	IPS	left	384	-45	-39	52	9.36
			445	-26	-63	30	8.20
			52	-26	-66	63	7.28
		right	599	42	-37	43	8.84
			693	20	-67	63	7.90
			71	29	-63	32	7.49
			143	35	-48	49	7.25
	IFG	right	299	53	6	25	9.23
		left	518	-44	3	25	8.87
	dmPFC	bilateral	779	6	20	51	8.80
	dlPFC	right	194	33	2	66	7.59
		left	310	-26	2	46	7.59
repeated > novel	AG	left	69	-53	2	45	7.25
	AG	right	1810	-51	-60	31	9.41
			967	59	-61	27	8.85
	dmPFC	left	124	-9	30	54	8.47
			104	-6	54	25	6.85
	PPL	right	566	68	-39	39	8.44
	PCC	bilateral	643	-5	82	33	7.86

		88	14	-49	33	7.18
SFG	left	113	-18	47	39	7.39

Table 2. fMRI stimulation effects. Active tDCS altered activity in the right inferior frontal gyrus (IFG) for novel compared to repeated stimuli using peak family-wise error correction $p_{FWE} < .05$. Please note that this correction method tests the significance of each individual voxel. The significance is thus representative, irrespective of its size. A larger cluster in the same region was also significant when using a cluster-based FWE correction instead (not shown).

Contrast	Region	Hemisphere	Cluster size (voxels)	x	y	z	T Score
active > sham							
novel > repeated	IFG	right	1	56	39	7	6.37
repeated>novel	n.s.						

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